NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 455

TOXICOLOGY AND CARCINOGENESIS STUDIES OF CODEINE (CAS NO. 76-57-3) IN F344/N RATS AND B6C3F$_1$ MICE

(FEED STUDIES)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice Regulations, and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. The interpretive conclusions presented in this Technical Report are based only on the results of these NTP studies. Extrapolation of these results to other species and quantitative risk analyses for humans require wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

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NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF

CODEINE

(CAS NO. 76-57-3)

IN F344/N RATS AND B6C3F$_1$ MICE

(FEED STUDIES)

NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
Research Triangle Park, NC 27709

August 1996

NTP TR 455

NIH Publication No. 96-3360

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

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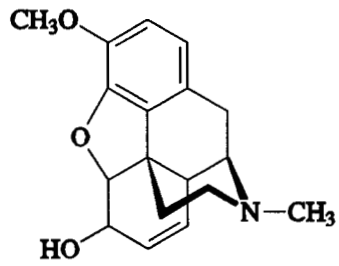
ABSTRACT



CODEINE
CAS No. 76-57-3
Chemical Formula: $C_{18}H_{21}NO_3$ Molecular Weight: 299.36

Synonyms: 7,8-didehydro-4,5-epoxy-3-methoxy-17-methylmorphinan-6-ol; methylmorphine; 3-*O*-methylmorphine monohydrate; *N*-methylnorcodeine; morphine-3-methyl ether; morphine monomethyl ether
Trade names: Codeinum, Codicept, Coducept, Metilmorfina

Codeine is used in a variety of pharmaceuticals including analgesics, sedatives, hypnotics, antiperistaltics, and antitussive agents. The National Cancer Institute and the Food and Drug Administration nominated codeine for study because it is a widely used drug and it is representative of the morphine class of compounds, for which chronic carcinogenicity studies had not been conducted. The oral route of administration was selected because it is the primary route of human exposure. Male and female F344/N rats and B6C3F$_1$ mice were given codeine (99% pure) in feed for 14 days, 13 weeks, or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium* and cultured Chinese hamster ovary cells.

14-Day Study in Rats

Groups of five male and five female F344/N rats were given 0, 1,562, 3,125, 6,250, 12,500, or 25,000 ppm codeine in feed for 14 days, which resulted in daily doses of approximately 125, 250, 450, 650, or 750 mg codeine/kg body weight to males and 125, 250, 500, 700, or 300 mg/kg to females. One female exposed to 6,250 ppm, one male and three females exposed to 12,500 ppm, and all males and females exposed to 25,000 ppm died during the study. Final mean body weights and mean body weight gains of all exposed groups except 1,562 ppm females were significantly lower than those of the controls.

No chemical-related gross lesions were observed in rats at necropsy. Thickening of the forestomach mucosa (hyperplasia and hyperkeratosis) and lymphoid depletion of the thymus in exposed males and females and testicular degeneration in exposed males, observed primarily in the 12,500 and 25,000 ppm groups, were associated with decreased survival and increased morbidity in these groups.

14-Day Study in Mice

Groups of five male and five female B6C3F$_1$ mice were given 0, 781, 1,562, 3,125, 6,250, or 12,500 ppm codeine in feed for 14 days, which resulted in daily doses of approximately 150, 300, 600, 1,300, or 3,000 mg codeine/kg body weight to males and 200, 400, 750, 1,500, or 3,000 mg/kg to females. All mice survived to the end of the study. The final mean body weight of 3,125 ppm females was significantly greater than that of the controls; the final mean body weight of 12,500 ppm females and the mean body weight gains of 12,500 ppm males and females were significantly lower than those of the controls.

Absolute and relative liver weights of 3,125, 6,250, and 12,500 ppm males and of 12,500 ppm females and the absolute and relative right kidney weights of 12,500 ppm males were significantly lower than those of the controls. No gross or histopathologic lesions were attributed to codeine exposure.

13-Week Study in Rats

Groups of 10 male and 10 female F344/N rats were given 0, 390, 781, 1,562, 3,125, or 6,250 ppm codeine in feed for 13 weeks, which resulted in daily doses of approximately 25, 50, 100, 200, or 450 mg codeine/kg body weight to males and 25, 50, 100, 250, or 500 mg/kg to females. There were no chemical-related deaths during the study. Final mean body weights and mean body weight gains of all groups of exposed males and of females exposed to 1,562, 3,125, or 6,250 ppm were significantly lower than those of the controls. Feed consumption decreased with increasing exposure concentration during the first week of the study; however, by the end of the study, feed consumption by most exposed groups was similar to that by the controls. There were alterations of various hematology and clinical chemistry parameters at the end of the study. There was a mild dose-dependent lymphopenia in females receiving 1,562 ppm and above and in 6,250 ppm males. There also was a minimal to mild macrocytosis that occurred in all exposed groups of males and in females exposed to 781, 3,125, or 6,250 ppm. No significant differences between control and exposed rats were observed in sperm morphology or vaginal cytology parameters.

Absolute and relative adrenal gland weights of exposed males and of 3,125 and 6,250 ppm females were significantly greater than those of the controls. Absolute and relative liver weights of exposed males were significantly lower than those of the controls. Relative thymus weights of 3,125 and 6,250 ppm males were significantly lower than that of the controls. No chemical-related gross or histopathologic lesions were observed in male or female rats.

13-Week Study in Mice

Groups of 10 male and 10 female B6C3F$_1$ mice were given 0, 390, 781, 1,562, 3,125, or 6,250 ppm codeine in feed for 13 weeks, which resulted in daily doses of approximately 60, 120, 260, 460, or 1,000 mg codeine/kg body weight to males and 60, 130, 280, 530, or 1,200 mg/kg to females. Two male mice in the 3,125 ppm group died during week 7. All other mice survived to the end of the study. Final mean body weights of exposed males and females were similar to those of the controls. Feed consumption by exposed males and females was similar to that by the controls. Abnormal posture was observed in all exposed groups of males. There were no significant differences in hematology or urinalysis parameters in male or female mice. Minor, sporadic changes occurred in a few of the clinical chemistry parameters; they were not considered biologically significant. No significant differences in sperm morphology or vaginal cytology parameters were attributed to codeine exposure.

Absolute and relative kidney weights of 3,125 and 6,250 ppm males were lower than those of the controls. No chemical-related differences in organ weights were observed in females. No chemical-related gross or histopathologic lesions were observed in male or female mice.

2-Year Study in Rats

Groups of 60 male and 60 female F344/N rats were fed diets containing 0, 400, 800, or 1,600 ppm codeine for up to 106 weeks, with 9 or 10 rats per group evaluated at 15 months. These exposure concentrations resulted in average daily doses of approximately 15, 30, and 70 mg codeine/kg body weight to males and 15, 40, and 80 mg/kg to females.

Survival, Body Weights, Feed Consumption, and Clinical Findings

Survival of 400 ppm females was significantly greater than that of the controls; survival of all groups of exposed males and of 800 and 1,600 ppm females was similar to that of the controls. There was an exposure-related decrease in mean body weights of males and females. The final mean body weight of 1,600 ppm males was 88% that of the controls, and the final mean body weight of 1,600 ppm females was 89% that of the controls. Feed consumption by exposed groups was similar to that by the controls. Chemical-related clinical findings were limited to ocular discharge in exposed males and females.

Pathology Findings

Absolute and relative adrenal gland weights of 800 and 1,600 ppm males were significantly greater than those of the controls at 15 months. There were no

increased incidences of neoplasms attributable to codeine exposure at any site. At 2 years, there were exposure-related decreases in the incidences of adrenal medulla hyperplasia in males and females. There was an exposure-related decrease in the incidence of benign pheochromocytomas in males, and the incidences in exposed males were significantly lower than that in the controls. In 1,600 ppm females the incidences of mammary gland fibroadenomas and of fibroadenomas or adenocarcinomas (combined) were significantly lower than those in the controls. The decreased incidences of benign pheochromocytomas in males and mammary gland neoplasms in females were considered to be related to codeine exposure.

2-Year Study in Mice

Groups of 60 male and 60 female B6C3F$_1$ mice were fed diets containing 0, 750, 1,500, or 3,000 ppm codeine for up to 106 weeks, with 9 or 10 mice per group evaluated at 15 months. These exposure concentrations resulted in average daily doses of approximately 100, 200, or 400 mg codeine/kg body weight to males and females.

Survival, Body Weights, Feed Consumption, and Clinical Findings

Survival of exposed males and females was similar to that of the controls. Mean body weights of 750 and 1,500 ppm males and females were similar to those of the controls throughout most of the study. Mean body weights of 3,000 ppm males and females were less than those of the controls from about week 13, and the final mean body weights of these groups were 86% and 82% those of the respective controls. Feed consumption by exposed groups was similar to that by the controls.

Pathology Findings

There were no increased incidences of neoplasms attributable to codeine exposure at any site. At 15 months, the incidence of thyroid gland follicular cell hyperplasia in 3,000 ppm males was significantly greater than that of the controls, and this lesion was observed in 1,500 and 3,000 ppm females. At 2 years, the incidences of follicular cell hyperplasia in all exposed groups of mice were significantly greater than those in the controls, but there were no increases in thyroid gland follicular cell neoplasms. The incidence of centrilobular fatty change in the liver of 3,000 ppm males was significantly lower than that in the controls at 15 months, and the decreased incidence appeared to be related to exposure level. At 2 years, the incidences of eosinophilic foci, foci of fatty change, centrilobular cytomegaly, and centrilobular fatty change in 3,000 ppm males were lower than those in the controls. The incidence of hepatocellular adenomas and the incidence of hepatocellular adenomas or carcinomas (combined) in 3,000 ppm males and females were significantly lower than those in the controls; this was considered to be related to lower body weights in these groups.

Genetic Toxicology

Codeine phosphate was not mutagenic in any of four strains of *Salmonella typhimurium*, with or without S9 metabolic activation enzymes. In cytogenetic tests with cultured Chinese hamster ovary cells, codeine phosphate induced dose-related increases in sister chromatid exchanges, with and without S9, only at concentration levels that caused cell cycle delay. No induction of chromosomal aberrations was noted in cultured Chinese hamster ovary cells treated with codeine phosphate, with or without S9.

Conclusions

Under the conditions of these 2-year feed studies, there was *no evidence of carcinogenic activity** of codeine in male or female F344/N rats exposed to 400, 800, or 1,600 ppm. There was *no evidence of carcinogenic activity* of codeine in male or female B6C3F$_1$ mice exposed to 750, 1,500, or 3,000 ppm.

Thyroid gland follicular cell hyperplasia was increased in exposed male and female mice.

Decreased incidences of benign pheochromocytomas of the adrenal medulla in male rats and mammary gland fibroadenomas and fibroadenomas or adenocarcinomas (combined) in female rats were related to codeine exposure.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 9. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 11.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Codeine

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Doses	0, 400, 800, or 1,600 ppm (approximately 15, 30, or 70 mg/kg in feed)	0, 400, 800, or 1,600 ppm (approximately 15, 40, or 80 mg/kg in feed)	0, 750, 1,500, or 3,000 ppm (approximately 100, 200, or 400 mg/kg in feed)	0, 750, 1,500, or 3,000 ppm (approximately 100, 200, or 400 mg/kg in feed)
Body weights	1,600 ppm group lower than controls	1,600 ppm group lower than controls	3,000 ppm group lower than controls	3,000 ppm group lower than controls
2-Year survival rates	29/50, 20/50, 21/50, 20/50	28/50, 38/50, 29/51, 32/51	41/50, 38/50, 45/50, 43/50	36/50, 36/51, 43/51, 35/50
Nonneoplastic effects	None	None	Thyroid gland: follicular cell hyperplasia (7/49, 25/50, 29/50, 34/50)	Thyroid gland: follicular cell hyperplasia (14/48, 29/51, 42/51, 44/50)
Neoplastic effects	None	None	None	None
Decreased neoplasm incidences	Adrenal medulla: benign pheochromocytoma (16/49, 6/50, 6/50, 3/50)	Mammary gland: fibroadenoma (27/50, 21/50, 27/51, 8/51); fibroadenoma or adenocarcinoma (30/50, 23/50, 29/51, 8/51)	None	None
Level of evidence of carcinogenic activity	No evidence	No evidence	No evidence	No evidence

Genetic toxicology

Salmonella typhimurium gene mutations:	Negative in strains TA97, TA98, TA100, and TA1535 with and without S9
Sister chromatid exchanges	
Cultured Chinese hamster ovary cells *in vitro*:	Positive with and without S9
Chromosomal aberrations	
Cultured Chinese hamster ovary cells *in vitro*:	Negative with and without S9

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence, including animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results (**clear evidence** and **some evidence**); one category for uncertain findings (**equivocal evidence**); one category for no observable effects (**no evidence**); and one category for experiments that cannot be evaluated because of major flaws (**inadequate study**). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Report series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following five categories is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to potency or mechanism.

- **Clear evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a chemical-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemical related.
- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemical-related increases in malignant or benign neoplasms.
- **Inadequate study** of carcinogenic activity is demonstrated by studies that, because of major qualitative or quantitative limitations, cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. Such consideration should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- adequacy of the experimental design and conduct;
- occurrence of common versus uncommon neoplasia;
- progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- combining benign and malignant tumor incidence known or thought to represent stages of progression in the same organ or tissue;
- latency in tumor induction;
- multiplicity in site-specific neoplasia;
- metastases;
- supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- presence or absence of dose relationships;
- statistical significance of the observed tumor increase;
- concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- survival-adjusted analyses and false positive or false negative concerns;
- structure-activity correlations; and
- in some cases, genetic toxicology.

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on codeine on June 20, 1995, are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing NTP studies:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On June 20, 1995 the Technical Report on the toxicology and carcinogenesis studies of codeine received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. J.K. Dunnick, NIEHS, introduced the toxicology and carcinogenesis studies of codeine by discussing the chemical's uses and the rationale for study, describing the experimental design, reporting on survival and body weight effects, and commenting on compound-related nonneoplastic lesions in mice. Dr. Dunnick also reported on toxicokinetic studies in rats and mice performed in collaboration with investigators at Burroughs Wellcome. The proposed conclusions for the 2-year studies were *no evidence of carcinogenic activity* in male or female F344/N rats or in male or female B6C3F$_1$ mice.

Dr. Taylor, a principal reviewer, agreed with the proposed conclusions. He observed that as noted in the Technical Report, the analgesic action of codeine depends on *O*-demethylation to morphine, a reaction that is mediated in humans by cytochrome P$_{450}$ IID6. He provided additional references and said the discussion on human metabolism of codeine should be expanded. Dr. Dunnick said the additional references would be included.

Dr. Miller, the second principal reviewer, agreed with the proposed conclusions. She asked for clarification regarding the significance of dose-related increases in sister chromatid exchanges occurring at concentrations that caused cell cycle delay in cultured Chinese hamster ovary cells. Dr. Dunnick said she would clarify these findings (page 56).

Dr. Vodicnik, the third principal reviewer, agreed with the proposed conclusions. She was pleased that toxicokinetic data were included (Appendix M).

Dr. A. Turturro, National Center for Toxicological Research, asked if some quantification could be added relating lower body weights with decreased incidences of mammary gland and adrenal gland neoplasms in rats. Dr. J. Haseman, NIEHS, responded that incidences of adrenal gland neoplasms were decreased at all three concentrations, including two that had no body weight differences. However, he said that decreased incidences of mammary gland neoplasms could in part be explained by lower body weight, and perhaps some quantification of the extent of this association could be added (page 59).

Dr. Vodicnik moved that the Technical Report on codeine be accepted with the revisions discussed and with the proposed conclusions as written for male and female rats and mice, *no evidence of carcinogenic activity*. Dr. Miller seconded the motion, which was accepted unanimously with nine votes.